

Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in inadvertently vaccinated healthy children

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ABSTRACT

Twenty-seven children aged seven months to 5 years were inadvertently vaccinated with a COVID-19 vaccine, the CoronaVac (Sinovac, China), an inactivated SARS-CoV-2 vaccine, in two different cities of Sao Paulo State, Brazil. After the event, these children were monitored by local pediatricians and serum samples were collected at the first visit and 30 days after vaccination and tested for SARS-CoV-2 S1 serology with Ortho total IgG anti-S1 protein and Cpass, an ACE2 receptor binding domain inhibition assay. Only one child had a mild symptom after vaccination, with no other adverse events documented up to the 30 days follow-up. Of 27 children tested 3-9 days after vaccination, 5 (19%) had positive serology suggesting a previous natural SARS-CoV-2 infection, with all 19 tested on day 30 after vaccination and presenting with positive tests, with an increment of antibody titers in those initially positive. A low Cpass binding inhibition was observed in the first collection in 11 seronegative cases, with high titers among those anti-S1 positive. All children showed an important increase in antibody titers on day 30. The event allowed the documentation of a robust serological response to one dose of CoronaVac in this small population of young children, with no major adverse effects. Although it was an unfortunate accident, this event may contribute with future vaccine strategies in this age group. The data suggest that CoronaVac is safe and immunogenic for children.

KEYWORDS: COVID-19 vaccines. Adverse events. Brazil.

INTRODUCTION

On May 22nd, 2021, 27 healthy children were inadvertently vaccinated with a COVID-19 vaccine CoronaVac, instead of receiving the influenza vaccine in a primary health care unit in Itirapina, a small city in the countryside of Sao Paulo State, Brazil. One day later (May the 23rd), the same error happened in Diadema, a city located in the metropolitan area of Sao Paulo city, where five children were also inadvertently vaccinated with CoronaVac.

CoronaVac is an inactivated SARS-CoV-2 vaccine developed by Sinovac Life Sciences (Beijing, China), which has been used among adults aged ≥ 18 years in Brazil, since January 2021. This vaccine is produced by Sinovac in partnership with the local public vaccine manufacturer Butantan¹. Over 40 million doses of CoronaVac had already been administered by the end of June 2021 all over the country².

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Received: 13 August 2021

Accepted: 4 October 2021

The vaccination error was promptly reported to the health department of each municipality and, in relation to adverse events, to the vaccination surveillance system. The Epidemiological Surveillance Center of Sao Paulo State (CVE) and the Adolfo Lutz Institute assisted the health departments of Itirapina and Diadema. The objectives were to describe the public health response to a programmatic error and to monitor the vaccine safety, tolerability and seroconversion by detecting the total amount of IgG antibodies against SARS-CoV-2 S1 spike protein after the vaccination of children with CoronaVac.

MATERIALS AND METHODS

The children who had been inadvertently vaccinated with CoronaVac (Sinovac Life Sciences, Beijing, China) were monitored by pediatricians in primary health care units for 30 days, to receive medical assistance if any sign or symptom appeared. Reports of their health conditions were sent to the health department of each municipality. Three visits were scheduled for medical evaluation, right after the event recognition (error in the vaccine used), at 15th and 30th day after vaccination. To inform the families and local health workers caring for these children of their serological status, two registered assays, available at State public laboratories were used. Blood samples were taken on the first medical evaluation (3-9 days after the event) and on the 30th day after the vaccination event. The presence of antibodies for SARS-CoV-2 were detected using (i) a chemiluminescent microparticle assay (VITROS® Anti-SARS-CoV2, Ortho Clinical Diagnostics, United Kingdom) which detects the domain of the S1 (spike) antigen, considering seroreactive for SARS-CoV-2 antibodies samples with titers >1.0 and; (ii) the evaluation of antibodies able to interfere with the RBD-ACE2 interaction (RBI), measured by cPass (SARS-CoV-2 Neutralization Antibody Detection kit, GenScript, USA), both test performed following the manufacturer's instructions. The test was considered positive for the presence of neutralizing antibodies for SARS-CoV-2 when an inhibition titer $\geq 20\%$ is obtained, and samples are assigned as presenting with low inhibition when percentages from 5% to 20% inhibition are detected.

All clinical information and laboratory tests results were registered in each case, reporting the clinical manifestations of adverse events to the health departments and to the programmatic error surveillance system.

The approach to these children occurred only after the detection of the error in the type of vaccine used, when their parents were contacted and informed about the vaccination error. All children were evaluated by local health workers and upon demand of parents and local health authorities,

blood samples were collected to perform the serological assays. Those that agreed to participate in the serological evaluation were oriented to return after 30 days after vaccination for retesting. The present investigation was the official response to a public health crisis, thus it did not require the approval of an ethical council.

RESULTS

Table 1 shows the characteristics of CoronaVac vaccinated children. From the total of 27 children, 52% were male, with ages ranging from 7 months to 5 years. Only one 2-years-old child presented a symptom (running nose) during the first visit, nine days after vaccination. No other symptoms were reported among the infants in the 30 days following the vaccination.

All children (n=27) were tested at the first visit for S1 antibodies and 5 (18.5%) had total S1 spike protein IgG titer higher than 1.0 (reagent tests) 3-9 days after vaccination. Nineteen had blood collected 30 days after vaccination and all of them had total S1 spike protein IgG titers higher than 1.0 (reagent tests). Four of the five children who presented reagent tests at the first visit were retested on the 30th day after vaccination, all showing an increased total IgG anti S1 spike protein, going from a mean of 10.4 to a mean value of 20.5. About half (47%, 9/19) tested for the receptor binding domain inhibition (RBI) showed results above 20%, but most had a low binding inhibition (5-20%), with only three cases, all S1 seropositive, with high titers (over 90% inhibition). On the 30th day, 12/13 tested children had titers above 30%, with a median titer of 45% (IQR 36-65). Titers of S1 have also increased from the initial collection up to the 30th day, from 0.1 (IQR 0-0.3) to 7.9 (5.5-11.2).

DISCUSSION

No COVID-19 vaccines are authorized in Brazil, so far, for use in children under the age of 12 years. However, a phase 2 study has already assessed the safety, tolerability and immunogenicity of CoronaVac in the population aged 3 to 17 years³.

We presented a response to a programmatic error situation. Despite the vaccination error, all monitored children did not show adverse events following the immunization. The analyses from phase 1-3 trials have shown that CoronaVac was safe in adults aged 18 years and older⁴. A Phase 1-2 study evaluated children and adolescents aged 3 to 17 years vaccinated with CoronaVac and showed that 27% of the vaccinated participants reported at least one adverse event within 28 days of vaccination³. All adverse

Table 1 - Demographic and serological results from children inadvertently vaccinated with CoronaVAc (one dose), Sao Paulo State, Brazil, 2021.

Sex	Age (months)	DV 1	DV 2	S1 Ab 1	S1 Ab 2	RBI 1	RBI 2
Female	22	4	NA	0.01	NA	5.00	NA
Female	28	4	30	0.00	6.49	19.61	30.95
Female	42	4	30	3.11	19.00	39.90	NA
Female	69	4	NA	0.01	NA	NA	NA
Female	44	4	30	0.00	7.53	-6.89	45.22
Female	30	4	NA	11.30	NA	NA	NA
Female	3	6	30	0.01	7.73	9.07	62.34
Female	60	7	NA	0.01	NA	NA	NA
Female	7	3	33	0.00	10.10	21.83	64.87
Female	37	3	33	0.00	3.03	3.60	33.04
Female	60	3	33	0.00	7.94	8.73	51.00
Female	54	9	NA	0.02	NA	NA	NA
Male	52	4	NA	0.01	NA	-0.69	NA
Male	31	4	NA	0.00	NA	NA	NA
Male	23	4	30	0.00	3.77	NA	22.05
Male	22	4	NA	0.03	NA	NA	NA
Male	60	4	30	5.17	20.50	91.50	96.8
Male	31	4	30	0.00	3.00	27.12	35.84
Male	46	4	30	0.00	10.20	-10.54	38.68
Male	10	4	30	0.00	8.90	22.99	68.12
Male	13	4	30	0.00	11.20	22.50	68.96
Male	49	4	30	0.01	4.19	13.21	35.79
Male	35	4	30	0.03	5.48	23.48	38.06
Male	32	4	41	0.01	9.73	NA	NA
Male	18	3	33	19.00	24.10	97.07	NA
Male	54	5	34	0.17	6.95	19.48	57.98
Male	23	9	30	13.30	18.60	97.36	NA

DV 1 = days after the 1st dose of vaccine and first blood sampling ; DV 2 = days after the 1st dose of vaccine and 2nd blood sampling; S1 Ab 1= antibody titers against the SPIKE domain S1 at the time of the 1st blood sampling ; S1 Ab 2 = antibody titers against the SPIKE domain S1 at the time of the 2nd blood sampling ; RBI 1 = percentage of receptor binding inhibition at the time of the 1st blood sampling ; RBI 2 = percentage of receptor binding inhibition at the time of the 2st blood sampling ; NA = not available.

events were non-severe, and the most common reactions were pain at the injection site and fever³.

All tested children showed an increase in total S1 spike protein IgG antibodies 30 days following the vaccination. Although some children already had antibodies at the time of the initial blood collection, presumably due to previous asymptomatic, unrecognized infection by SARS-CoV-2. When these previously positive children were tested 30 days after the vaccination, they showed an increment in IgG binding antibody units at the second blood sampling. As no infection during the observation period was documented, and if they had occurred, they would unlikely affect all children, one can assume that the immunological response was generated by the vaccine. The receptor binding

inhibition, a functional assay to evaluate the ability of serum samples to interfere with the binding of the viral receptor binding domain of the S1 protein with the cellular receptor ACE-2, showed some inhibition (from 5 to 20%) in 11 children that did not had total anti S1 IgG antibodies⁵. The titers were however low and may represent either unspecific reactivity or a previous exposure to other coronaviruses. The limited information of the test in particular in this age group, does not allow us to come to any conclusion, but all retested children on the 30th day after vaccination showed important increments in RBI titers, with only one case below 30% inhibition as can be seen in Table 1. These two assays have been evaluated in comparison with other diagnostic tests and have shown an adequate performance⁶. Although

limited to a serological response to S1 antigens, either total IgG to the viral S1 protein binding inhibition to the major SARS-CoV-2 receptor, the data suggest an anti-spike response after one dose of the vaccine. In other words, one dose of CoronaVac was immunogenic in children³.

Wrong vaccine administration is the most reported vaccination error^{7,8}. CoronaVac and influenza vaccines used in the Brazilian public health system come from the same local producer (Butantan) and they have the multiple dose presentation, which could favor the confusion. However, the label and the color of the bottle cap are different. The current high number of different vaccines available in the Brazilian immunization schedule demands well trained health professionals. Vaccination errors may harm patients and cause a negative impact on the population's confidence on vaccination, which in turn will negatively impact the vaccination coverage⁸.

This study has some limitations. Firstly, it is a response to an unexpected event, justifying the small sample size that does not allow us to rule out the occurrence of rare adverse events or even to definitely conclude on the duration of the seroconversion observed after the first dose. Secondly, children did not receive the second dose and were not evaluated after the end of the proposed immunization. Thirdly, the cellular immunity was not evaluated. Finally, the monitoring period (30 days) was short to determine long-term immunogenicity and also for a complete evaluation of safety.

Children infected with SARS-CoV-2 mainly have mild disease or are asymptomatic, when compared with adults. However, a small number of children, especially those with health comorbidities, might be at risk of severe COVID-19^{9,10}. Furthermore, the SARS-CoV-2 infection can lead to a serious, although rare complication called the multisystem inflammatory syndrome in children¹¹. Finally, children can be transmitters of SARS-CoV-2 in communities¹². A vaccine against SARS-CoV-2 for children and adolescents will contribute decisively to the control of the COVID-19 pandemic. Our investigation suggests that CoronaVac is well tolerated and safe and can induced humoral responses in children, but proper safety and effectiveness studies must be performed before expanding the vaccination to young children.

ACKNOWLEDGMENTS

The authors would like to thank all the collaborators from the Health Departments of Diadema and Itirapina, the GVE – Santo Andre and Piracicaba (regional surveillance offices), and the regional laboratories of Santo Andre and Rio Claro, Instituto Adolfo Lutz.

AUTHORS' CONTRIBUTIONS

EGF, HKS, NVDLA, MLBRN, and LFMB conducted the investigation together with the technicians of the municipality of Diadema and Itirapina; GISL, VOS, RY, KCRM, JFG, JAL, and LFMB performed the laboratory assay; EGF drafted the initial manuscript. GISL, HKS, NVDLA, and LFMB reviewed the manuscript. All authors approved the final manuscript as submitted.

CONFLICT OF INTERESTS

None.

FUNDING

None.

REFERENCES

1. São Paulo. Centro de Vigilância Epidemiológica “Prof. Alexandre Vranjac”. Divisão de Imunização. Documento técnico: campanha de vacinação contra a COVID-19: 23 de julho de 2021, 18ª atualização. [cited 2021 Nov 5]. Available from: https://portal.saude.sp.gov.br/resources/cve-centro-de-vigilancia-epidemiologica/vacina/documentos-tecnicos-covid-19/documentotecnico_campanhadevacinacaocontraacovid_18atualizacao_23_07.pdf
2. Brasil. Ministério da Saúde. LocalizaSUS. [cited 2021 Nov 5]. Available from: <https://localizasus.saude.gov.br/>
3. Han B, Song Y, Li C, Yang W, Ma Q, Jiang Z, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy children and adolescents: a double-blind, randomised, controlled, phase 1/2 clinical trial. *Lancet Infect Dis*. 2021 In Press.
4. Zhang Y, Zeng G, Pan H, Li C, Hu Y, Chu K, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect Dis*. 2021;21:181-92.
5. Taylor SC, Hurst B, Charlton CL, Bailey A, Kanji JN, McCarthy MK, et al. A new SARS-CoV-2 dual-purpose serology test: highly accurate infection tracing and neutralizing antibody response detection. *J Clin Microbiol*. 2021;59:e02438-20.
6. Tan SS, Saw S, Chew KL, Huak CY, Khoo C, Pajarillaga A, et al. Head-to-head evaluation on diagnostic accuracies of six SARS-CoV-2 serological assays. *Pathology*. 2020;52:770-7.
7. Morse-Brady J, Marie Hart A. Prevalence and types of vaccination errors from 2009 to 2018: a systematic review of the medical literature. *Vaccine*. 2020;38:1623-9.

8. Braga PC, Silva AE, Mochizuki LB, Lima JC, Sousa MR, Bezerra AL. Incidence of post-vaccination adverse events in children. *J Nurs UFPE Online*. 2017;11 Suppl 10:4126-35.
9. Zimmermann P, Curtis N. Coronavirus infections in children including COVID-19: an overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. *Pediatr Infect Dis J*. 2020;39:355-68.
10. Maltezou HC, Magaziotou I, Dedoukou X, Eleftheriou E, Raftopoulos V, Michos A, et al. Children and adolescents with SARS-CoV-2 infection: epidemiology, clinical course and viral loads. *Pediatr Infect Dis J*. 2020;39:e388-92.
11. Ebina-Shibuya R, Namkoong H, Shibuya Y, Horita N. Multisystem inflammatory syndrome in children (MIS-C) with COVID-19: insights from simultaneous familial Kawasaki disease cases. *Int J Infect Dis*. 2020;97:371-3.
12. Kao CM, Orenstein WA, Anderson EJ. The importance of advancing severe acute respiratory syndrome coronavirus 2 vaccines in children. *Clin Infect Dis*. 2021;72:515-8.